Editorial

Executive summary with focus on pediatrics: therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: a revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society and the Society of Infectious Diseases Pharmacists

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Pharmacokinetic and outcomes studies on vancomycin have emerged in neonates and pediatrics since the publication of the first adult-focused consensus guideline for the therapeutic monitoring of vancomycin in 2009. Developed by a committee representing the American Society of Health-Systems Pharmacists, Infectious Diseases Society of America, the Society of Infectious Diseases Pharmacists and newly-integrated Pediatric Infectious Diseases Society, this updated consensus revision evaluates the current evidence and scientific data associated with vancomycin dosing and monitoring for serious methicillin-resistant *Staphylococcus aureus* (MRSA) infections and provides new recommendations based on recent available evidence in neonates infants and children, with extrapolation of adult data when pediatric studies are limited (*Tables 1*,*2*).

The previous consensus guidelines recommended a trough target of 15–20 mg/L to facilitate the management of patient therapy and simplify dose adjustment and monitoring. However, since the implementation of this recommendation, reports of increased risk of nephrotoxicity have been published in both pediatrics and adults, especially when trough level monitoring was applied. Notably, this trough target was not the primary pharmacokinetic/pharmacodynamic (PK/PD) target in the original outcomes

Table 1 Grading system for recommendations based on quality of evidence

Category and grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for or against use
B	Moderate evidence to support a recommendation for or against use
C	Poor evidence to support a recommendation
Quality of evidence	
I	Evidence from 1 or more properly randomized controlled trials
II	Evidence from 1 or more well-designed clinical trials, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

Adapted from the Canadian Task Force on the Periodic Health Examination (1).

studies; it only served as a surrogate marker for the area-under-the-curve over-24-hour to minimum inhibitory concentrations (AUC/MIC) target of 400 mg·h/L that was statistically associated with improved clinical outcomes in adults with MRSA infections. In addition, since the publication of the first consensus guideline, neonatal and pediatric studies have demonstrated that vancomycin AUC/MIC, compared with trough concentrations, is a realistic target that acknowledges the impact of the MIC's of vancomycin from the child's MRSA isolate. In fact, one of every four children who actually achieved the AUC/MIC target exposure were still below the previously-recommended trough target of 15–20 mg/L, placing these children at risk for increased and unnecessary exposure if subsequent therapeutic dosing was based on measured trough concentrations. Importantly, an AUC/MIC of 400 was shown to correspond to trough concentrations of ~7–11 mg/L in neonates and children. Recently, PK/PD and toxicodynamic studies have also demonstrated a significantly reduced risk of vancomycin nephrotoxicity when AUC/MIC monitoring was employed versus traditional trough monitoring. In light of these considerations, the approach to monitoring vancomycin therapy by AUC/MIC rather than trough concentrations, is believed to be the safer and more pharmacokinetically-accurate goal that ensures the use of the minimum effective dose of vancomycin in neonates, infants and children.

Assuming that the clinical and microbiologic outcomes with vancomycin therapy for serious MRSA infections are similar for children and adults, the extrapolation of outcomes studies in adults is reasonable until prospective, comparative outcomes data in children using AUC/MIC vs. trough concentration monitoring are presented. As such, dosing in children should be designed to achieve an AUC/MIC of 400 based on serum exposure of vancomycin. However, vancomycin exposures at the site of infection with MRSA in children (osteomyelitis, pneumonia/empyema, pyomyositis) may actually require higher serum exposures (potentially up to 600 mg·hr/L for a MIC of 1 mg/L) but no data exist for outcomes with a range of defined exposures at different tissue sites. Renal function [and therefore vancomycin clearance (CL) is also more robust] in children than adults, suggesting that an increased weight-based dose may be required to achieve a similar exposure in adults and thus provides additional support for the need for early monitoring of vancomycin exposure. The PK/PD target of AUC/MIC of 400 has been widely used by investigators to model pediatric dosing and therapeutic monitoring. With no PK/PD studies and outcomes data to support the higher exposure (AUC/MIC of 600) in pediatrics, it is reasonable to aim for an AUC/MIC 400 in pediatrics to limit the development of exposure-related acute kidney injury (AKI). With the variability of vancomycin serum exposure noted in children given an identical dose, linked to the variability of vancomycin MIC's in MRSA, an AUC/MIC-guided approach to monitoring and dosing, preferably using two post-dose concentrations with Bayesian estimation to ensure the use of the minimum effective dose, is recommended.

Similar to adults, the aggregate literature in pediatrics suggests that the risk of nephrotoxicity increases as a

Table 2 Primary recommendations for vancomycin dosing and therapeutic drug monitoring*

A. Adults and pediatrics

1. In patients with suspected or definitive serious MRSA infections, an individualized target of the AUC/MIC_{BMD} ratio of 400 to 600 (assuming a vancomycin MIC_{BMD} of 1 mg/L) should be advocated to achieve clinical efficacy while improving patient safety (A-II)
2. When transitioning to AUC/MIC monitoring, clinicians should conservatively target AUCs for patients with suspected or documented serious infections due to MRSA assuming a vancomycin MIC_{BMD} of 1 mg/L or less at most institutions. Given the importance of early, appropriate therapy, vancomycin targeted exposure should be achieved early during the course of therapy, preferably within the first 24 to 48 hours (A-II). As such, the use of Bayesian-derived AUC monitoring may be prudent in these cases since it doesn't require steady-state serum vancomycin concentrations to allow for early assessment of AUC target attainment
3. Trough only monitoring, with target between 15–20 mg/L, is no longer recommended based on efficacy and nephrotoxicity data in patients with serious infections due to MRSA (A-II). There is insufficient evidence to provide recommendations on whether trough only or AUC-guided vancomycin monitoring should be used among patients with non-invasive MRSA or other infections
4. Vancomycin monitoring is recommended for patients receiving vancomycin for serious MRSA infections to achieve sustained targeted AUC (assuming a MIC_{BMD} of 1 mg/L, unless it is known to be greater or less than 1 mg/L by BMD). Independent of MRSA infection, vancomycin monitoring is also recommended for all patients at high risk of nephrotoxicity (e.g., critically-ill patients receiving concurrent nephrotoxins), patients with unstable (i.e., deteriorating or significantly improving) renal function, and those receiving prolonged courses of therapy (more than 3 to 5 days). We suggest the frequency of monitoring be based on clinical judgement; frequent or daily monitoring may be prudent for hemodynamically unstable patients (e.g., end stage renal disease) and once-weekly monitoring for hemodynamically stable patients (B-II)
5. Based on current national vancomycin susceptibility surveillance data, under most circumstances for empiric dosing, the vancomycin MIC should be assumed to be 1 mg/L. When the MIC_{BMD} is >1 mg/L, the probability of achieving an AUC/MIC ≥400 target is unlikely with conventional dosing; higher doses may risk unnecessary toxicity and the decision to change therapy should be based on clinical judgement. In addition, when MIC_{BMD} <1 mg/L, we do not recommend decreasing the dose to achieve the AUC/MIC target. It is important to note the limitations in automated susceptibility testing methods, including the lack of precision and variability in MIC results depending on method used (B-II)
6. The pharmacokinetics of continuous infusion suggest that such regimens may be a reasonable alternative to conventional intermittent infusion dosing when the AUC target cannot be achieved (B-II)
7. Incompatibility with vancomycin and other drugs commonly co-administered in the ICU requires the use of independent lines or multiple-catheters when vancomycin is being considered for continuous infusion (A-III)

D. Pediatrics

1. Based on an AUC target of 400 mg·hr/L (but potentially up to 600 mg·hr/L assuming MIC of ≤1 mg/L) from adult data, the initial recommended vancomycin dosage for children with normal renal function and suspected serious MRSA infections is 60 to 80 mg/kg/day, divided every 6 to 8 hours, for children ages 3 months and older (A-II)
2. The maximum empiric daily dose is usually 3,600 mg/day in children with adequate renal function (C-III). Most children generally should not require more than 3,000 mg/day and doses should be adjusted based on observed concentrations to achieve the AUC/MIC target. Early monitoring of observed concentrations is recommended when doses exceed 2,000 to 3,000 mg/day (A-III). Furthermore, close monitoring of observed concentrations and renal function is prudent in patients with poor or augmented renal CL as resolution of their renal function may occur within the first 5 days of therapy
3. AUC-guided therapeutic monitoring for vancomycin, preferably with Bayesian estimation, is suggested for all pediatric age groups, based on developmental changes of vancomycin CL documented from the newborn to the adolescent. Based on current available data, the suggestion for AUC-guided monitoring in pediatrics aligns with the approach for adults, including the application of Bayesian estimation for one trough concentration, or first-order PK equations with two concentrations (B-II). The Bayesian AUC-guided dosing strategy may be an optimal approach to individualize vancomycin therapy in pediatrics since it can incorporate varying ages, weights, and renal function. Both serum concentrations of vancomycin and renal function should be monitored since vancomycin CL and creatinine CL are not always well correlated in pediatrics. Furthermore, aggressive dosing to maintain target AUC exposure and decrease the risk of potential AKI in treatment of MRSA infection necessitates drug monitoring

Table 2 (*continued*)

Table 2 (*continued*)

4. Therapeutic monitoring may begin within 24 to 48 hours of vancomycin therapy for serious MRSA infections in children, as in adults (B-III). Any delay in therapeutic monitoring should be based on severity of infection and clinical judgment. Dosing adjustment should be made for those with renal insufficiency, obesity, or for those receiving concurrent nephrotoxic drug therapy. Following the initial dose, dosing adjustment is important for those with acute renal insufficiency, but subsequent adjustment (particularly within the first 5 days of therapy) may be necessary for those experiencing recovery of renal function. Sustained or subsequent decreases in dosage may be needed, particularly for those with chronic renal insufficiency and those receiving concurrent nephrotoxic drug therapy (B-III)
5. Vancomycin exposure may be optimally maintained below the thresholds for AUC of 800 mg·hr/L and trough concentrations of 15 mg/L to minimize AKI (B-II). The safety of vancomycin above 80 mg/kg/day has not been prospectively evaluated. Avoiding vancomycin doses ≥100 mg/kg/day is suggested since they are likely to surpass these thresholds (B-III)
6. Insufficient data exist on which to base a recommendation for a loading dose among the non-obese pediatric population. Loading doses from adult studies may be considered, but further studies are needed to elucidate the appropriate dose for the various pediatric populations from the neonate to adolescent (C-III)
7. Pediatric obesity: data suggest that obese children are likely to have vancomycin exposures that may be statistically greater than normal weight children when doses are calculated on a mg/kg basis, but these differences are not known to be of sufficient clinical importance to suggest different mg/kg empiric vancomycin dosages in obese children at this time. Similar to non-obese children, obese children <12 years old, compared with those ≥12 years, may require higher mg/kg dose (B-II)
8. Pediatric obesity: therapeutic monitoring is likely to be of particular value in obese children, both for therapeutic response and the risk of AKI. The specific recommendations for therapeutic monitoring in non-obese children may also apply for obese children (B-II). A loading dose of 20 mg/kg by total body weight is recommended in obese children (A-III)
9. Neonates: doses recommended to achieve an AUC of 400 mg·hr/L (assuming a MIC of 1 mg/L) in neonates and infants up to 3 months old range from 10 to 20 mg/kg every 8 to 48 hours, depending on post-menstrual age, weight and SCr (A-II)

*, Refer to the complete vancomycin consensus guideline for recommendations specifically for adults. MRSA, methicillin-resistant *Staphylococcus aureus*; AUC, area-under-the-curve; MIC, minimum inhibitory concentration; BMD, broth microdilution; CL, clearance; AKI, acute kidney injury; SCr, serum creatinine.

function of vancomycin exposure, especially when trough concentration exceeds 15–20 mg/L. A continuous exposure-response relationship for toxicity was also observed with AUC; even after adjusting for stay in the intensive care unit and concomitant use of nephrotoxic drugs, AUC ≥800 mg·hr/L was independently associated with an increased risk of AKI. The linkage of AUC to nephrotoxicity, along with the strong correlation between AUC and trough concentrations reinforces AUC as a reasonable PK/PD parameter for therapeutic monitoring that encompasses both therapeutic exposure and toxic responses. For situations in which vancomycin MIC's are 2 or greater, often requiring doses above 80–100 mg/kg/day to achieve the AUC/MIC exposure of 400, alternative antibiotics active against MRSA should be considered.

Recent studies highlight the importance of estimating AUC values through Bayesian techniques to improve the accuracy in predicting vancomycin exposure-outcomes and safety in patients. To best estimate a specific patient's exposure profile, Bayesian-guided monitoring quantifies the sequential relationship between the population-based "prior" of an individual patient's PK parameter values (Bayesian prior) and the revised patient's PK parameter values derived using exact dosing and drug concentration data (Bayesian conditional posterior). The advantages of this monitoring approach are three-fold: (I) early collection of concentrations within the first 24 to 48 hours, rather than waiting until steady-state conditions; (II) incorporation of factors that account for "dynamic" changes that may occur in critically-ill patients to optimize effect and predict future dosing; and (III) generation of accurate and reliable estimates of daily AUC values using trough-only PK sampling (albeit the preferred method is two post-dose serum concentrations of peak and trough to improve safety).

Almost all data available on vancomycin PK/PD and toxicodynamics have been derived from patients who have been treated for serious infections caused by MRSA; we believe that these data should not be routinely applied to non-serious MRSA infections, and to less virulent organisms causing other infections (e.g., Staphylococcus epidermidis in neonates) that may require vancomycin therapy. The recommendations in the revised guideline should not

replace sound clinical judgement in managing patients who require vancomycin therapy. Specific details pertaining to empiric and definitive treatment dosing in neonates, children and obese children, along with optimal monitoring of AUC, are provided in the Guidelines (2). The complete vancomycin guideline can be cited and accessed via https://academic.oup.com/ajhp/advance-article/doi/10.1093/ajhp/zxaa036/5810200.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. The periodic health examination. Canadian Task Force on the Periodic Health Examination. Can Med Assoc J 1979;121:1193-254.
2. Rybak MJ, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant Staphylococcus aureus infections: a revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm 2020;77:835-64.

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